507 Eugenia Ave.

Nov. 9, 1954

Dear Francis:

Thank you very much for letting me see these mss. In the absence of the figures, I did not try to read them with any deeply critical intent, but I think I did follow the argument without any trouble. I think, myself, that you are perhaps a bit hard on Newcombe, re phenotypic lag, though of course you are quite right that the empirical distribution has not been completely explained.

Luca and I have run into another factor in the indirect selection experiments that may be of interest to you. (One factor, when we had changed media for incidental reasons, was an adaptive mutation on the sensitive component that led to a cycle of periodic selection and subverted our efforts to enrich for the mutants further in that series!) This is variability in lag and early increase from single cells, (especially in mixed cultures?). To try to explain fluctuations in enrichment ratios, Luca set up inocula containing about .3 resistant and 10^7 sensitive, and assayed at saturation. There was a remarkable dispersion in the number of resistants (new mutations were negligible). I don't know whether this will be unique for the present case, where the mutant has a growth rate only about 85-90% of the wild type; I think it would be instructive to do more experiments simply on the early growth of very small inocula. Kendall has, of course, brought up the subject, but only hypothetically. I suspect that the dispersion of lags might be skewed in such a way as to contribute materially to the Lurian variance.

Yours, as ever,

Joshua Lederberg